Quarterly Progress Report

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Neural Prosthetic Control

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Contents

This Quarterly Report is organized into five sections. First there is a summary of the overall objectives of the contract. In the subsequent three sections we describe the goals and activities of the three main components of the project: Array development, development of decoding algorithms, and development of interfaces. Each section has, at its end, a description of the progress made during the current quarter on that phase of the project. Lastly, we describe project goals for the upcoming quarter.

1. Introduction

A number of neurological disorders, such as spinal cord injury, MD and ALS result in the inability to make voluntary movements. A major reason for paralysis in these disorders is a disconnection of the signal from a normal brain from the spinal cord or muscles. Devices that can detect and decode motor commands have the potential to restore voluntary actions in these individuals. The purpose of this project is to demonstrate the ability to use neural signals to control real world devices in monkeys; such devices can ultimately serve as prosthetic aids for paralyzed individuals.

Control signals for prosthetic devices can be derived from a number of sources, including the eyes, muscles, and EEG. These signals are, however, rather limited in the number of dimensions they can control. Going beyond a one dimensional control signal is difficult and often interferes with natural behavior. For example, two dimensional EEG control requires full attention to control without distraction (such as gaze shifts). By contrast, populations of neurons appear to contain rich signals, potentially able to control multiple dimensions. However, chronic recording of multiple neurons in primates has been technically challenging, the ability to decode neural activity into meaningful control signals is poorly understood and the ability to control devices using such signals is not developed.

The overall goal of this work is to develop a means to bring a robotic arm under near real time neural control using a multineuron signal derived from a recording device that is chronically implanted in a macaque monkey motor cortex. This project has three specific objectives. The **first objective** is to develop and test technologically advanced neural recording devices in a non-human primate model. This work examines the stability, efficiency and biocompatibility of electrode arrays and the suitability of the primary motor cortex as a sight to obtain neural recordings. Once recorded, neural activity must be decoded into meaningful control signals. The optimal methods for such decoding are not obvious. A **second objective** of the project is to examine various decoding methods and evaluate their ability to be useful control signals. This requires mathematical tools and signal processing that reconstructs intended actions from abstract, neurally based motor commands generated in the cortex. This aspect of the project involves fundamental motor control questions, such as what coordinate system is used to encode voluntary actions. **A third objective** of this project is to show that such signals can be used to control devices such as a robotic arm or a computer interface. These devices serve as a proxy for the lost limb and can be used to recreate useful actions like those intended for the arm. Successful completion of these goals would suggest that this approach could be used to restore movement in paralyzed humans.

2. Summary of Achievements this quarter Significant progress was made in all three objectives during the past quarter. During this period we implanted four arrays in two monkeys, further developed methods to enhance the speed of training monkeys for use in array testing, and perfused one monkeys (B164) for histological processing. Data was collected to test decoding. A CRS robot arm was ordered, delivered and set up. Histological material examined showed that arrays produce little gliotic response after months in place. We continued development of neural decoding methods, including new probabilistic methods and established a working group with Professor Michael Black of Computer Science, Elie Bienenstock of Applied Mathematics and graduate students Yun Gao and Mijial Serruya. Our analyses revealed that hand position could be recovered from linearly filtered spike trains using small numbers of neurons. During this period the University extensively renovated the laboratory to provide more suitable space that is required for training monkeys. This renovation delayed training during this period, but other aspects of the project were continued as renovations were carried out.

3. Array Development

The goal of the array development of this aspect of the project is to identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex. This requires monkey training in various behavioral tasks, implantation using various modifications in the surgical procedures and in the array assembly and recording to test the quality and stability of units.

3.1 Behavioral training In order to test for motor related neural activity, monkeys are first operantly conditioned to the various arm movement tasks using juice or water reward. Animals are motivated to perform these tasks by restricting access-time to fluids. During training and recording periods, monkeys are allowed as much fluid as they wish to obtain when they perform the training tasks. Fluids are also supplemented after training sessions and on weekends. as approved by the institutional animal care committee. Training tasks are also support the animals' psychological well being because they provide an additional sources of challenge which is rewarded. Some delay in training occurred because of laboratory renovations. This delayed surgical implantation because animals were not sufficiently trained to go forward with an array implant.

3.1.1 Radial direction task: Monkeys are first operantly conditioned (using juice or water reward) to perform an instructed-delay task consisting of visually-guided planar reaching movements from a central holding position to a radially located target (Figure 3). Animals move a two-joint manipulandum in the horizontal plane to direct a cursor from a central hold position to one of eight possible radially positioned targets (6 cm away from start position) viewed on a computer monitor. Hand position is recorded as the x and y location of the manipulandum using a digitizing tablet, with a sampling rate of 200 Hz. The tangential velocity and acceleration of the hand is computed by numerical differentiation using own custom software. A trial is composed of three epochs: a "hold" period during which time the monkey maintains the cursor at the hold position for 0.5 s, a random 1-1.5 s "instructed delay" period during which the target for the forthcoming action appeared but movement is withheld, and a "go" period initiated by target blinking (mean reaction time ~365 ms). Manipulandum position is monitored using a digitizing tablet sampled at 72 Hz. During this period five monkeys are being trained on this task.

3.1.2 Continuous tracking task: This task has been developed by our laboratory for a systems analysis approach to describe neural encoding in MI. It overcomes numerous shortcomings of step tracking tasks: correlation of kinematic variables and nonstationarities in behavioral and neural data. This makes it possible to treat each neural spike as an independent sample from a process with a known distribution, a requirement for many statistical tests and for information theoretic analysis. This task uses the same 2 dimensional device as the direction task except that the stimulus must be tracked in a continuous fashion. We generate a broad distribution of movement stimuli that monkeys must track. Data from this task are used to create the linear filters used to test our ability to reconstruct hand motion from neural data.

Our approach is to have the monkey move its hand (the end point effector) across a two dimensional workspace such that the probability distribution of each kinematic variable is as broad as possible (i.e. the monkey will make a series of motions that will, over time, include all possible velocities, positions, etc., within a plane of movement.) For this task monkeys are trained to track a visual target (2 degree white circle on black background) on a computer screen. The target motion is computer controlled to move in a pseudorandom, experimenter determined fashion. The statistics of the motion of the target, and the resultant tracking motion of the monkey's hand, are chosen in such a way that the entropy (the accepted measure of "broadness") of the distribution of motion is maximized under the constraints imposed by reaction time and biomechanical properties of the arm. In other words, the monkey moves its hand so that we sample from the complete space of possible planar arm movements. We hypothesize that it will be possible to mimic the arm kinematics with a prosthetic device (robot arm) by building a series of decoding filters that defines the relationship between the set of kinematic variables and arm movement. Because we have simultaneously recorded neurons, we can use not only the firing rate of each cell, but also the joint or higher order distribution (e.g. covariance) of neuronal activity to extract information about natural, time-varying movement parameters. During this period we further developed software to control this task and collect kinematic data. Three monkeys were also trained to perform this task.

3.1.3. Button box task. The button task has been developed as a simple version of the radial task (3.1.1) task that can be learned quickly so that monkeys can be made available for testing arrays. Task training is the major rate limiting step to array implantation, since monkeys must be trained before this surgery occurs. This task simply requires the monkey to press one illuminated button arranged in a circle around a central button Buttons are illuminated with a red LED to indicate which button to press for a reward. During training monkeys are shaped to hold to the center button for a 1-4 second random delay, then one peripheral button is illuminated as the target and as a go signal. Successful pressing of the illuminated button is reinforced with liquid. The devices we have developed are introduced in the cage, then monkeys perform the same task in the primate chair, where recordings are performed. A student was hired to help with fabrication of the boxes.

3.2 Array Implantation*:* Arrays are implanted in the MI arm representation, medial to the spur of the arcuate sulcus, abutting the central sulcus. The ability to locate arm related neurons using these sulcal landmarks has been 100% successful in our tests. The UEA microelectrode arrays consist of 100, 1.0mm long platinized tip, silicon probes arranged in a square grid on 400μm centers. Impedances between 50-500 kΩ (1 nA, 1kHz sine wave)

(Nordhausen et al., 1996). Arrays are wired to connectors contained in a custom designed titanium percutaneous pedestal with using 1 mil gold, Teflon insulated wire (the assembly is custom fabricated for us by Bionics). Two extra wires (50.8 μm diameter, Pt-Ir 20%) with approximately 5.0 mm of the terminal insulation removed are inserted subdurally and used as reference and as backup. The bundle of gold wires is coated with silicone elastomer (MDX4-4210, Dow Corning, MI). The back of the array and percutaneous connectors are coated with silicone elastomer to mechanically protect the wires and maintain electrical insulation at the bond pad sites.

The array is inserted rapidly into the cortex using a calibrated, pneumatically propelled mass, and typically, the array is and cortical surface is covered by a Teflon sheet. The dura is then loosely closed and this area is covered by a sheet of Gortex followed by silicon elastomer. Finally the entire region is covered with cranioplast cement which is anchored to the skull through a series of titanium bone screws. (see Figure 1.). During this period we implanted 4 arrays in two monkeys (B003 and 99-8)using no foreign bodies except the array and a Timesh cap.

3.3 Array development: Connector technology has severely limited the number of electrodes we able to use address for recording. The generally available connector from Bionics was a 12 pin Microtek, which allowed only connection to only 11 electrodes of the 100 available in the array. To increase recording to 22 we used two of these connectors. Subsequently we adopted a Winchester 50 pin connector.

Bionic developed a new generation of 45 pin connectors, called the Tulip connector which was based on an edge card connector. With two of these connectors we can achieve 74 connections (with two references). While these connectors have several undesirable features (the connector profile is high, the edge card is easily damaged), this has been the only high density connector available in the project to date. All of these connectors failed due to design flaws, resulting in no recordings from these two monkeys. In one case we found that the connector had rotated in the pedestal, thereby shearing all of the wires. In the other case the gold contacts shorted to each other, so that no signals were obtained. The rotation problem has been addressed by BTI by inserting a set screw that prevents rotation of the connector in the pedestal. However, we have urged BTI to generate new, more reliable high density connectors. They are in the development phase of such connectors. New, low insertion force connectors have been devised by Bionics and we are still expecting delivery in summer. 2001. Further implantations with the tulip connector were delayed while we evaluated their reliability.

3.4 Array Testing

Impedance High impedances have the advantage of providing high signal to noise ratio, but the tip must be close to a neuron to obtain recordings. On the other hand, a low impedance electrode detects many cells, making it difficult to isolate neurons from background 'hash'. The goal of this part of the project is to identify the optimal impedances for UIEA. During this project period, we began to examine the relationship between electrode impedance and the ability to detect and isolate single units on an electrode. We are evaluating electrode impedances from 50 – 1000 kΩ\, which constitutes the range of impedances that occur across the arrays we have received. Preliminary data indicate that impedance is not critical to obtain useful single neuron recordings.

Recording Stability: The ability to maintain the same cells each day of recording by the UA is not known and is important in the design of a prosthetic device. Decoding algorithms must be able to deal with instabilities. To measure stability similarity measures including the autocorrelation function (to determine firing pattern), movement related activity, directional tuning properties, and spike waveform. This data is being analyzed by Dr. Hatsopoulos and Dr. Kenji Nakata, a neurosurgical resident at Brown working in the lab during his research year.

Tethering Forces Original observations on the UIEA suggested that the wire bundle from the array to the connector provided significant tethering forces, causing the electrode to move and, hence, damage the cortex. Our initial UEA versions were tested with only 11 of the 100 possible wires attached. We have now tested arrays with 11, 21, 47, or 74 wires have been attached to the 100 possible in the array. Across all of the experiments the yield of usable units has been ~30-40% of the active electrodes and this appears to be independent of the number of wires. Thus, we conclude that tethering forces are not a significant factor in determining electrode yield.

Head stabilization: Lack of head stabilization has created a number of difficulties in recording. Movement of some versions of the array connectors (notable the ribbon cable connectors to the preamplifiers required for the Tulip connectors) produce significant electrical artifact that obliterates recording signals. Some monkeys rotate in their chair which results in damage to the cabling. During this project period we identified an appropriate head restraint system, purchased necessary components from Thomas Recording. This introduced some delays in implantation and testing because we needed to design and manufacture head posts and then implant each monkey. The posts provided with the Thomas system were not sufficiently strong to hold the head. We redesigned the posts and identified a local machinist to manufacture these new posts and pedestals. Head post surgery requires at least a six week period to allow integration of the posts into the skull. In addition, the initial version of the headposts had small bases that were not sufficiently stable. In this quarter we redesigned the head post base and fabricated them. During this quarter we implanted four monkeys with head bolts.

3.5 Histological analyses*:* The goal of histological analysis is to determine tissue reaction to the UIEA. We test for cell loss and reaction using both thionin cell stain and GFAP, to test for glial reactivity. During this quarter we carried out qualitative examination of tissue from B164. This analysis indicates that there is minimal tissue effects of the array over time. Several months after implantation there is little glial reaction, as measured by GFAP reaction product. Long term biocompatibility is also demonstrated by the ability to record neurons for years on these arrays. Neurons were recorded in one monkey over 1098 days. By qualitative measures these neurons appear to be no different in their properties from those recorded in acute preparations using single microelectrodes. Our histological sections reveal that UIEA arrays do, sink ~100 or more μm into the cortex, compressing the upper cortical layers; the functional effect of this is not detectable in our neural recordings. We examined tissue from one monkey implanted with 4 arrays using different closing methods. All arrays revealed sinking, with indentation of the cortex. GFAP staining reaction product was sparse in all cases (with arrays in place 3 months); Nissl staining showed some compression of the upper cortical layers, but otherwise the tissue did not show strong gliotic reaction. Damage from the implantation where the bone flap was replaced was evident, but in the area around

the bone edge, not at the array. This served as a positive control for the GFAP reaction which was strong under the damaged zone at the bone edge.

3.6 Recoding Technology Development. We are working with Dr. Richard Normann's group at the University of Utah to modify one of the Bionics 100 channel recording/acquisition systems so that it can classify spikes in real time and provide output to a second computer. A second computer is used to decode the spike patterns, both to build movement classification models and for online classification. Working with Richard Normann and BTI we modified the current BTI spike acquisition device so that it is capable of providing 'spike times' in real time to the decoding computer. This system was set up and used to pass data from the recording system to a second computer system which is used to build spike models and to decode activity in real time. We also finished adapting our Plexon data acquisition system to pass discriminated spikes for online classification. Further advantages of the Plexon is that is has a higher sampling rate for more accurate spike discrimination.

4. NEURAL DECODING

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The goals of this aspect of the project are to determine: whether we can recover the hand trajectory using the activity of multiple MI neurons; how reliable this reconstruction will be; how many simultaneously recorded neurons are required; can the computation be performed fast enough to be used in a prosthetic device; and finally can the reconstruction algorithm be made adaptive enough that it will withstand changes in the functional properties of recorded neurons as may result for instance from motion of the implant between successive days or weeks (see above). In this project period, we tested the ability for linear regression methods based upon small numbers of neurons to provide estimate of any hand trajectory. This work was largely completed in this period. In a second step we have begun to examine non-parametric Bayesian methods with the goal of achieving trajectory reconstructions that can have greater speed and more accuracy compared to linear reconstructions.

Previous work has shown that neural discharge in motor cortex is related to a number of kinematic variables, including direction, position, acceleration and velocity (Georgopoulos and Ashe, 1994; Fu et al., 1993). However, these analyses have been restricted to simple evaluations of discrete, usually scalar, variables studied in tasks in which monkeys must only move from a single point to one of a few static targets; We term this a discrete (as opposed to a continuous tracking task). Because of technical limitations, cells in these earlier studies were recorded one at a time. Information underlying cortical movement control contained in the mutual activity of populations of neurons is not available from the available single electrode data; extraction of this information requires observation of not one, but many simultaneously recorded neurons. Further, just as the visual or auditory processing can not be described by single discrete parameters, the rich structure and fluidity of natural movements can not be captured by specifying, for example, average direction of hand motion over hundreds of milliseconds. Neural control of movement proceeds continuously, and satisfactory description of natural movements requires simultaneous knowledge of

multiple time-varying parameters; we term tasks that require continuous movement under visually guided or internal control *continuous tasks*.

4.1` Linear Decoding: This approach consists in regressing separately the *x* and *y* coordinates of hand position (or velocity) at time *t* on the observed spike counts of the simultaneously recorded neurons in a window of variable length around time *t*, suitably discretized. For instance, by discretizing a window of length 1sec into bins of length 50ms each, we get 20*N* explanatory variables, where N is the number of neurons. Mathematically and computationally, this regression is straightforward: it simply solves for the least-squared-error linear solution. This allowed us to explore systematically the quality of the reconstruction that this method provides for a wide spectrum of discretization schemes, ranging from 1 to 30 bins around time *t*, with either identical or different widths (allowing, in particular, a finer resolution near time *t*). We used both causal and non-causal schemes (in the former, observations are allowed only before time t).

The performance of this linear filtering method has been assessed by cross-validation, using three different criteria: the L2 distance between the observed and the reconstructed positions; the fraction of the variance of the observed position accounted for by the reconstruction; the correlation coefficient between the observed and reconstructed positions. It is not clear which of these is optimal and methods of error evaluation are being investigated.

4.2 Non-Parametric Decoding Algorithms The simple linear-filtering approach mentioned above does not provide a probabilistic interpretation of the data that can facilitate analysis and support the principled combination of multiple sources of information. Previously used probabilistic approaches such as Kalman filtering do not suffer from this drawback, yet it should be noted that with a small number of cells our interpretation of the neural data may be ambiguous and the posterior probability of the kinematic variables, given the neural activity, may be best modeled by a non-Gaussian, possibly multi-modal, distribution. Clearly, Kalman filtering is inadequate under these conditions, and a non-parametric approach is called for. Thus, to cope with these issues in a sound probabilistic framework, we started to investigate a non-parametric ways in which this approach might be implemented in neural data.

Estimating the Conditional Firing Maps We view the neural firing activity recorded during training as a stochastic and sparse realization of some underlying model that relates neural firing to hand motion or hand position. Each plot (for a given cortical cell) can be thought of as a type of "tuning function," or "receptive field," which characterizes the "response" of the cell given hand velocity or position. However, since the data is very noisy and sparse, we need to compute an optimal estimate of these receptive fields by an appropriate smoothing of the "training" data.

In previous work, investigators have considered a variety of strict models of the tuning function of neurons, including a cosine tuning function (Georgopoulos et al. 1986) and a modified cosine function (Moran and Schwartz 1999). We have explored various non-parametric approaches to model a neurons properties and, adopting a Bayesian formulation, constructed a Maximum *A Posteriori* (MAP) estimate of a cell's conditional firing. In this case we use data from the cell's firing itself to determine a probabilistic model of the cell's tuning function, rather than assume some strict model. The data for this approach requires the broad sampling produced by the continuous task; the non-stationarities and irregular

sampling of discrete tasks are not sufficient or appropriate to generate statistical representations of the tuning functions. We compare the various models using cross-validation to test against the ability of the decoding schema to deal with any set of new data. . It is expected that this approach will provide a richer movement signal than can obtained in parametric models and will allow the use of statistical methods to evaluate how well the decoding performs.

Our non-parametric models are related to Markov Random Fields (MRF) (Geman and Geman 1984), and our plan is to include a spatial *prior* probability, which encodes our expectations about the variation of neural activity in velocity or position space. The MRF prior states that the expected firing at a given velocity depends only on the firing at neighboring velocities. We are currently examining ways to implement these non parametric models and compare them with parametric models .

4.3 Further issues We expect that after the model(s) is (are) suitably trained we will be able to control the movement of the robot arm in real time, using the decoding provided by the model, i.e., the most likely sequence of states that is computed and continuously updated given the observed simultaneous spiking processes. One problem may be occur if the set of neurons changes during the course of day-to day testing. Using probabilistic decoding we can establish real time checks of the decoding reliability. If error bounds are exceeded, we can initiate a recalibration sequence. This will be part of future efforts.

5. Interface development The goals of this aspect of the project are (5.1) to develop interfaces with peripheral devices (i.e., robot arm, computer), (5.2) demonstrate that decoded neural signals can be used to control such peripheral devices, and (5.3) demonstrate that monkeys can bring this signal under near real time control.

5.1 Interface with peripheral devices In this quarter we to developed software to transform hand trajectory coordinates into signals that move position cursors on a computer monitor and our CRS robot arm. We demonstrated that both a robot arm or computer cursor can be used to mimic actual hand motion using data processed offline.

5.2 Offline control of prosthetic devices*:* During this period Ammar Shakouni, an engineering MS student, began a project to write software in Labview to transform the neurally decoded trajectory signals into commands for the CRS robot arm. An connection from the decoding computer to the robot control computer was also established.

5.3 Real time Control of prosthetic devices: We did not address this goal during this project period.

5.4 Arm paralysis/Control without feedback. The goal is to demonstrate that monkeys are able to control the robot arm using neural activity when arm actions are impossible and sensory feedback is missing, a condition that mimics human paralysis. This will be achieved by blocking the brachial plexus with injection of sodium channel blockers (lidocaine, Klein et al., 1998). This procedure can be used reversibly to eliminate all movement and sensation from the arm for a period of hours. The method is used safely and repeatedly in humans for surgical procedures as well as chronically (Lierz et al., 1998), so it represents minimal risk to the health or well being of the monkey. It is a reasonable substitute for arm amputation which is a more invasive way to demonstrate that motor cortical neural activity can be used for control when the effector member is missing. We began discussions with local physicians and the University veterinarian for the optimal methods to achieve blockade.

6.0 Plans For Next Quarter

1 Array Development

- **Behavioral Training:** We will continue behavioral training and add 6 monkeys to the training schedule so that they can be implanted. Some time will be lost as we continue to move in to new laboratory space and have additional equipment built to enhance our training capabilities.
- **Button box task** Button boxes software will be completed and a new computer interface will be completed that will allow control of cage trainers by one PC. Software will be written to allow behavioral control using a PC (current version Mac based). Three monkeys will be trained to perform the button box version of the radial task using this apparatus. Three monkeys will continue being trained to perform the radial task using this apparatus, and two more monkeys will begin training for the first time. Two monkeys will continue chair training with the button box for recording purposes.
- **Radial task & Continuous tracking.** Two monkeys are continuing to train in these tasks for recording purposes.
- **Arrays/implantation & Surgical Procedures** One implantation is planned for a tulip array, to be used for decoding and interface studies, but other surgeries are being delayed in anticipation of the new 100 pin connectors.
- **Array development.** The major advance in array development in the next quarter will be the testing of the new connector. If surgical procedures can be performed during the next quarter, we expect testing of these arrays to begin by in the late part of the subsequent quarter.
- **Array testing** We will continue to recordings from the one monkey that has high quality recordings and continue recordings from the monkey implanted in Q7.
- **Perfusion histology** We will examine processed tissue from monkeys that were perfused and processed this period.

2. Neural Decoding

a. Linear Reconstruction; We will test the day to day stability of linear decoders by using filters established on one day for the next days data set.

b. Other methods; Drs. Bienenstock and Black will continue to evaluate methods that use probabilistic inference to decode neural activity. We are submitting a manuscript on the probabilistic approach to decoding to Neural Information Processing for peer review and acceptance for presentation at the meeting in Fall, 2001.

3. Interface Development

a. Peripheral devices interfaces. Mr. Shakouni will complete and improve software to drive the robot arm.

b. Offline control We will use recorded data, decode it and use this as a control signal to control the robot arm and to control a cursor on a PC. We will begin to evaluate the error in time a positioning between actual arm position and the decoded position.

c. Real Time control. Mr. Serruya will evaluate the ability for monkeys to control a position feedback cursor for a behavioral task. Monkeys trained on the continuous tracking task will be tested to determine whether they can continue to perform a tracking task when the position feedback cursor is fully driven by real time decoded neural activity.

d. Arm paralysis/control without feedback. We will test injection methods to achieve arm paralysis.